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| EXAMINER | |
|---|---|
| JEAN-LOUIS, SAMIRA JM | |

| ART UNIT | PAPER NUMBER |
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| 1627 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,424 | CHEN ET AL. | |
| | Examiner | Art Unit | |
| | SAMIRA JEAN-LOUIS | 1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02/12/10, 06/01/10, 07/09/10, and 09/30/*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *22-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/23/06, 04/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Claims 1-54 are currently pending in the application.

Applicant's election with traverse to compound 173 and election of group I in the reply filed on 09/30/10 is acknowledged. The traversal is on the ground(s) that compound 173 is indeed encompassed by formula (I), that claim 1 is a linking claim, and that the claims relate to a single general inventive concept. The Examiner acknowledges that compound 173 is indeed encompassed by formula (I) and thus the species election in the reply filed on 07/09/10 was indeed responsive. However, the traversal that claim 1 is a linking claim and that the various groups delineated in the office action dated 06/16/10 share common technical features is again unpersuasive. This is not found persuasive because the claims recited in the instant application recite a multiplicity of groups that do not relate to a single generative concept. While the claims of group I are directed to treating kinase dependent diseases, the claims of group II are directed to disorders associated with uncontrolled cellular activities. Group III's technical feature is focus on screening for compounds that are modulator of Tie-2 while group IV is directed to inhibiting proliferation and group V to actual inhibition of Tie-2. As a result, the Examiner maintains that the aforementioned groups of invention do not relate to a single general inventive concept and consequently result in a lack of unity of invention. Regarding the species election, the examiner still maintains that the species possess contrasting structures where Y could be at least two nitrogens as

opposed to a single nitrogen in one of the ring and wherein A & B can all be various atoms (i.e. C or N) and would thus cause such species not to relate to a single general inventive concept (i.e. based on the functional groups described above, the aforementioned compounds would not possess a common core structure). As a result, the Examiner contends that such species do not share common technical features and thus lack unity.

Thus, the requirement is still deemed proper and is therefore made FINAL.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Claims 22-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected group and species, there being no allowable generic or linking claim. Claims 1-21 are examined on the merits herein. Additionally, the Examiner acknowledges that the elected species is free of the art. Thus, the search has been expanded to non-elected species.

***IDS***

The information disclosure statements (IDS) submitted on 02/23/06 and 04/30/09 are acknowledged and have been entered. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating certain kinase dependent cancers, does not reasonably provide enablement for the treatment of all kinase dependent diseases using a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, or prodrug thereof. The instant specification fails to provide information that would allow the skilled artisan to practice the treatment of all kinase-dependent diseases or conditions.

In re Sichert, 196 USPQ 209 (CCPA 1977)

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue

experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, or prodrug thereof. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Bennett who teaches that C-Jun-N-terminal kinase (JNK) plays a role in respiratory disease and yet applicant has not demonstrated effectiveness of the compounds of formula I in either inhibiting JNK or in treating respiratory diseases as delineated in the claims (see Bennett, abstract).

2. The breadth of the claims

The claims are thus very broad insofar as they recite the "treatment of all kinase-dependent diseases or conditions". While such "treatment" might theoretically be possible for some kinase-dependent diseases or conditions, as a practical matter it is nearly impossible to achieve a treatment for all possible kinase-dependent diseases or conditions with the same compound.

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[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the use of the compounds of formula (I) in treating all kinase-dependent diseases or conditions. No reasonably specific guidance is provided concerning useful therapeutic protocols for the treatment of all kinase-dependent conditions, other than inhibition of Tie-2, a receptor known to be involved in some cancers. The latter is corroborated by the working table 2 in the specification, pgs. 80-91.

The instant disclosure provides no evidence to suggest that this unique activity can be extrapolated to all kinase-dependent diseases such as respiratory disease or even to all cancers, for example, having unrelated mechanisms of action, and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard thereto.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed compounds could be predictably used for the treatment of all kinase-dependent diseases or conditions as inferred by the claims and contemplated by the

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"experimentation".

specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making hydrates or prodrugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically

acceptable salt, hydrate, or prodrug thereof. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention.

Attention is directed to *In reWands,* 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, or prodrug thereof. The relative skill of those in the art is high, that of a PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Vippagunta et al. who teach that predicting the formation hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice is both complex and difficult. All compounds respond differently to possible formation of hydrates. Consequently,

Vippagunta et al. teach that generalizations cannot be made for a series of compounds and their respective solvates (see Vippagunta et al., Advanced Drug Delivery Reviews, 2001, Vol. 48, pg. 18, section 3.4) and applicant fails to provide enablement support. As for prodrugs, the Examiner contends that making prodrugs is difficult and challenging and thus one skilled in the art would not readily envisaged how to make such prodrugs. While applicant refers to esters and amides as potential prodrugs, the specification (see pg. 53, paragraph 0128) teaches that the prodrugs of these novel compounds are not solely limited to such derivatives and thus envisioned other compounds as prodrugs. However, attention is directed to Beaumont et al. who teach the difficulties in obtaining prodrugs for oral delivery including ester prodrugs (Current Drug Metabolism, 2003, Vol. 4, pgs. 461-485). In fact, Beaumont et al. teach that designing ester prodrugs for oral delivery is a difficult undertaking and requires robust screening sequence in order to address the problems in maintaining aqueous solubility, lipophilicity, and chemical stability while enabling rapid and quantitative release (see Beaumont et al., Conclusion, pgs. 482-483, right col., last paragraph). Consequently, the Examiner maintains that in light of the fact that the compounds of formula (I) are novel and in light of the disclosure of Beaumont, synthesizing these novel prodrugs are not within the grasp of the skilled artisan absent a clear teaching of their synthesis.

2. The breadth of the claims

The claims are thus very broad insofar as they a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a

pharmaceutically acceptable salt, hydrate, or prodrug thereof, yet applicant fails to provide enablement on how the synthesis of the hydrates and prodrugs of compounds of formula (I) will be accomplished as previously mentioned.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification is not adequately enabled as to how to make a hydrate and provides no direction or guidance for a method to synthesize the prodrugs of the aforementioned compounds. In fact, applicant provided no guidance on how to obtain the aforementioned hydrates of the compounds of formula (I). As a result, countless experimentation would be necessary to obtain hydrates of formula (I) as claimed by applicant.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed hydrates and prodrugs of formula (I) could be predictably made as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation in order to obtain the hydrates of the aforementioned

compounds claimed by applicant, with no assurance of success.

Genentech, 108 F.3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Thus, in the absence of working examples there is no showing that the instant compounds will form hydrates. Since it is clear that merely bringing the compound into contact with water or a solvent does not result in a hydrate, additional direction or guidance is needed to make them and the specification has no such direction or guidance. Therefore, only the chemically structurally defined chemicals, but not the full breadth of the claims meet the enablement requirement provision of 35 USC § 112, first paragraph.

Therefore, a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, or prodrug thereof is not considered to be enabled by the instant specification.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

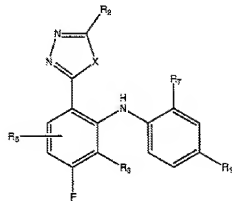
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

**Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Biwersi et al. (WO 2004/056789 A1).**

Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Biwersi et al. teach MEK inhibitors OXA- and THIA-Diazol-2-yl phenylamine compounds and derivatives and pharmaceutical compositions and methods for their use in proliferative diseases such as cancer (see abstract, pg. 2, lines 26-30, pg. 8, lines 31-33, pg. 9, lines 1-7, and pg. 100, lines 10-19). In particular, Biwersi et al. teach that MEK enzymes are dual specificity kinases involved in proliferative diseases such as cancer and that proliferative diseases are caused by a defect in the intracellular signaling system or the signal transduction mechanism of certain proteins (see pg. 1, lines 1-7). Additionally, Biwersi et al. teach compounds of the following structure:



or pharmaceutically acceptable salt or ester thereof (see pgs. 3-5). Specifically, compound 136 of Biwersi et al. read on instant compounds of formula (I) wherein all Y are equal to =CH-; 1 of A and B are –N=, 1 of A is NH and 1 of A is -C(H)=; L is C2 alkylene; X is NR3 wherein R3 is H; and Z is a substituted heterocyclyl (i.e. oxadiazole; see pg. 69, compound 136).

Accordingly, Biwersi et al. anticipate claims 1-4 and 6.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 7-9 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Biwersi et al. (WO 2004/056789 A1).**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The Biwersi et al. reference is as discussed above and incorporated by reference herein. However, Biwersi et al. do not teach R4 as an optionally substituted heteroaryl C1-C6 alkyl.

However, the Examiner contends that extension by one carbon chain (i.e. CH2 heteroaryl) is obvious to one skilled in the art. Moreover, the Examiner contends that homologs are considered to be obvious absent unexpected results. In re Henze, 85 U.S.P.Q. 261, 263, (C.C.P.A> 1950 ).

A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and/or similar utilities. "An obviousness rejection based on similarity in chemical structure and/or function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254

(CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to extend the carbon chain by one carbon since such extension is obvious and would have yielded similar results since such compounds are homologs of compound 136. Given the teachings of Biwersi et al., one of ordinary skill would have been motivated to formulate the compound of Biwersi et al. as a C1alkyl heteroaryl with the reasonable expectation of providing a method that is effective in treating proliferative diseases such as cancer.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samira Jean-Louis/

Examiner, Art Unit 1627

11/27/2010